

Applicant : Yurino, et al.  
Serial No. : 09/459,712  
Filed : December 13, 1999  
Page : 6



Attorney's Docket No.: 07898-053001 / PH-710US

## REMARKS

### **Status of the Claims**

#### *Pending claims*

Claims 1 to 7 are currently pending.

#### *Restriction Requirement and Election*

The Patent Office alleged that the application as filed was directed to two separate and distinct inventions; the two inventions were grouped as follows:

- I. Claims 1 to 6, drawn to methods of hybridization detection, classified in Class 435, subclass 6.
- II. Claim 7, drawn to a probe containing biochip, classified in Class 422, subclass 68.1.

Applicants elected Group I, claims 1 to 6. Claim 7 was withdrawn from further consideration in response to Applicants' election of Group I.

#### *Claims canceled and added in the instant amendment*

Claims 1 to 6 were canceled, without prejudice, and new claims 8 to 24 are added. Thus, after entry of the instant amendment, claims 8 to 24 will be pending.

#### *Outstanding Rejections*

Claims 1 to 6 stand rejected under 35 U.S.C. §112, second paragraph. Claims 1 to 4 and 6 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,023,540 to Walt et al. (hereinafter "Walt").

Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

### **Support for the Claim Amendments**

The specification sets forth an extensive description of the invention in the new claims. Support for new claims directed to a method for detecting the degree of binding between a probe and a sample comprising a biopolymer can be found, inter alia, on page 3, line 23, to page 4, line 26. Support for new claims wherein the detectable label comprises a fluorescent

material can be found, inter alia, on page 3, line 23, to page 4, line 26. Support for new claims wherein the emission wavelength of the fluorescent material labeling the sample biopolymer is detected separately from the emission wavelength of the fluorescent material labeling the probe can be found, inter alia, on page 4, lines 1 to 6. Support for claims wherein the sample biopolymer comprises a nucleic acid, such as a DNA or an RNA, e.g., is a hybridization reaction, or a protein, can be found, inter alia, on page 4, lines 17 to 19. Support for claims wherein the substrate on which each of a plurality of types of probes are immobilized at a given position comprises a biochip can be found, inter alia, on page 5, lines 15 to 17.

Figure 8 as filed has been replaced a substitute Figure 8. No new matter has been added. The new Figure 8 corrects an inadvertent error in Figure 8C, which has misplaced "balloon" positions.

#### **Issues under 35 U.S.C. §112, 2<sup>nd</sup> paragraph**

Claims 1 to 6 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite.

##### *The terms "nucleic acid" and "sample"*

The Patent Office alleges that the metes and bounds of the sample practice as compared to the claimed method of hybridization detection in the claims are vague and indefinite. Clarification via clearer claim working was requested.

Applicants believe the instant amendment addresses the Patent Office's concerns.

##### *The terms "bound" and "hybridization"*

The Patent Office alleges that use of the terms "bound" and "hybridization" in the claims is confusing. Clarification via clearer claim working was requested.

Applicants believe the instant amendment addresses the Patent Office's concerns.

##### *The phrase "detecting the hybridization between probe and sample"*

To paraphrase, the Patent Office alleges that use of the phrase "detecting the hybridization between probe and sample" in claim 1 and use of the phrase "value determined" in the claim 2 is confusing. Claim 6 also was alleged to have a confusing conflict between what is

being determined versus what is set forth in the claim. Clarification via clearer claim working was requested.

Applicants believe the instant amendment addresses the Patent Office's concerns.

It is believed that with the instant amendment addresses the Patent Office's concerns and the rejections to claims 1 to 6 under section §112, 2<sup>nd</sup> paragraph, can be properly withdrawn.

### **Issues under 35 U.S.C. §102(e)**

Claims 1 to 4 and 6 stand rejected under 35 U.S.C. §102 (e) for allegedly being anticipated by Walt, filed March 14, 1997.

The Patent Office cites Walt for allegedly disclosing the preparation and use of fiber optic sensors with microspheres attached on the surface.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

Walt discloses the development of a bead-based analytic chemistry system in which beads carrying different chemical functionalities may be mixed together while the ability is retained to identify the functionality of each bead using an optically interrogatable encoding scheme; and an optical fiber sensor in which the separate beads or microspheres may be optically coupled to discrete fibers or groups of fibers within the bundle.

The Patent Office alleges that the both the probe and sample analyte amounts are determined in Walt. For example, the Patent Office cited column 15, lines 16 to 40, for the disclosure of genosensors wherein the subpopulations of microspheres are determined, which is a determination of the number and corresponding the amount of microsphere/probe combinations on the fiber optic bundle surface.

However, while Walt's system may quantify the number of microspheres present on a fiber optic bundle surface, or determine which subpopulation a microsphere belongs to and how many microspheres belong to a subpopulation, it does not quantify the number of probes immobilized on each microsphere, as does the claimed invention. For example, in the cited

column 15, lines 16 to 40, various antibodies were affixed to the surface of microspheres. While the number of microspheres was measured, the number of antibody molecules per microsphere was not determined.

The Patent Office cited column 15, lines 16 to 40, for allegedly disclosing the normalization of signal caused by the target binding to the microspheres as required by pending claim 2. However, column 15, lines 16 to 40, does not teach or suggest quantifying the number of probes immobilized on each microsphere, quantifying the number of analytes bound to each microsphere, and comparing, or "normalizing," these amounts.

The Patent Office further cited column 11, lines 1 to 14, for allegedly describing the decoding of the microspheres after noting which microspheres changed their optical signature. Walt teaches that by identifying the chemical functionalities of the microsphere in which the optical signature has changed, using the encoded dye combinations, information regarding the chemical identity and concentration of the analyte may be gained based upon the interaction or non-interaction of each functionality contained in the probe. However, Walt does not teach or suggest quantifying the number of probes immobilized on each microsphere, quantifying the number of analytes bound to each microsphere, and comparing, or "normalizing," these amounts.

While Walt uses the term "normalizing" in column 15, lines 26 to 30, it is used in a different context than that used to describe Applicants' invention. As used in Walt, column 15, lines 26-30, the "normalizing" refers to the finding of a background signal. In other words, in Walt, a reading is taken and used to calculate the background noise of a reaction. Hence, subsequent images use this background "normalizing" signal as the level of background noise.

In contrast, the claimed methods not only quantitatively determine the amount of the sample target (e.g., a nucleic acid) bound (e.g., hybridized) in each spot of a biochip (e.g., a DNA microarray), they also determine the amount of the probe that was the basis of the binding (e.g., hybridization) taking place in each "spot" of the array; thus, it is possible to quantitatively determine the degree of binding (e.g., hybridization) between each probe and each sample target (e.g., a nucleic acid). The instant invention addresses an unavoidable problem found in the manufacture of arrays, or "biochips," where there are variances in the amounts of the probe (e.g., DNA sequences) immobilized onto a given position on a substrate surface (e.g., in a

hybridization assay using a DNA array, a plurality of types of probes are separately immobilized to a given position). Using the methods of the instant invention, by determining the amount of a probe that was the basis of a binding reaction (e.g., a hybridization) in each spot, it makes it possible to quantitatively determine the degree of hybridization between each probe and "target sequence," e.g., sample nucleic acid.

In contrast, as discussed above, in Walt, quantitative determination relating to microspheres is performed using fluorescence to determine which subpopulation a microsphere belongs to and how many microspheres belong to what subpopulation. Walt does not teach or suggest determining the amount of probe on each microsphere or the calculation of a normalized value for the binding between sample target and immobilized probe.

Applicants respectfully aver that these remarks and the instant amendment address the Patent Office's concerns and the rejections to claims 1 to 6 under 35 U.S.C. §102 (e) can be properly withdrawn.

### **CONCLUSION**

Claims 1 to 6 are pending in the application. Applicants request that the Examiner reconsider the application and claims in light of the foregoing reasons and instant amendment and withdraw the rejections to the claims under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §102 (e), and respectfully submit that the claims are in condition for allowance.

Applicants believe that no fees are necessitated by the present Response. However, in the event any fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050.

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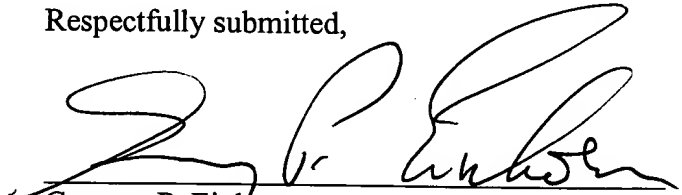
Attorney's Docket No.: 07898-053001 / PH-710US

If a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues toward placing the application in condition for allowance.

Respectfully submitted,

Date:

*August 01, 2007*



Gregory P. Einhorn  
Reg. No. 38,440

Fish & Richardson P.C.  
4350 La Jolla Village Drive, Suite 500  
San Diego, CA 92122  
Telephone: (858) 678-5070  
Facsimile: (858) 678-5099



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

Applicant : Yurino, et al.                      Art Unit : 1631  
Serial No. : 09/459,712                      Examiner : Arden Marschel, Ph.D.  
Filed : December 13, 1999  
Title : HYBRIDIZATION DETECTION METHOD AND BIOCHIPS

*In The Specification:*

A paragraph has been added to the specification, inserted in page 1, after the title.

Figure 8 as filed has been replaced with a substitute Figure 8.

*In The Claims:*

Claims 1 to 6 have been canceled, without prejudice.

Claims 8 to 24 have been added.

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